

**Til orientering er Paracet 125 mg suppositorier markedsført i Danmark med norske pakninger og norsk indlægsseddel. En dansk indlægsseddel for Paracet 125 mg kan findes på www.indlægsseddel.dk**

 **15 January 2024**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Paracet, suppositories**

**0. D.SP.NO.**

33801

**1. NAME OF THE MEDICINAL PRODUCT**

Paracet

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each suppository contains 60 mg paracetamol.

Each suppository contains 125 mg paracetamol.

Each suppository contains 250 mg paracetamol.

Each suppository contains 500 mg paracetamol.

Each suppository contains 1 g paracetamol.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Suppositories

White, torpedo-shaped suppositories.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Paracet is indicated for short-term treatment of fever, for example with colds and influenza, and mild to moderate pain, for example headache, toothache, menstrual pain, muscle pain and joint pain. Prevention under medical supervision of complications in high fever, prolonged headaches and muscle and joint symptoms.

**4.2 Posology and method of administration**

Posology

*Adults and children 40-50 kg (over 12 years):*

1-2 × 500 mg suppositories up to 4 times a day, but no more than 3000 mg in the course of 24 hours. An interval of at least 4-6 hours should be left between doses.

*Adults and children over 50 kg (over 12 years):*

1-2 × 500 mg suppositories or 1 × 1 g suppository up to 4 times a day. The maximum daily dose is 4000 mg. An interval of at least 4-6 hours should be left between doses.

In adults with severe liver disease, liver cirrhosis, chronic malnutrition or concurrent chronic alcohol abuse, 2 g paracetamol per day should not be exceeded (see sections 4.4 and 4.5).

*Paediatric population*

For children, the dose should be calculated individually based on the child’s weight.

Infants aged under 1 month:

Administer approx. 15 mg/kg body weight up to 3 times a day. An interval of at least 8 hours should be left between doses. The maximum daily dose is 60 mg/kg body weight.

To simplify, the guideline doses are divided into weight classes:

3-6 kg (under 1 month): 1 × 60 mg suppository up to 3 times a day

Children aged over 1 month:

Administer approx. 15 mg/kg body weight up to 4 times a day. An interval of at least 4-6 hours should be left between doses. The maximum daily dose is 75 mg/kg body weight.

To simplify, the guideline doses are divided into weight classes with an approximate indication of age:

4-6 kg (1-5 months): 1 × 60 mg suppository up to 4 times a day

7-12 kg (5 months-2 years): 1 × 125 mg suppository up to 4 times a day

13-25 kg (2-7 years): 1 × 250 mg suppository up to 4 times a day

26-39 kg (7-12 years): 1 × 500 mg suppository up to 4 times a day

Absorption from rectal administration is variable and often poorer than with oral use.

The lowest effective dose necessary to achieve efficacy should be used, and for the shortest possible treatment time.

Method of administration

Rectal use. Suppositories are to be inserted in the rectum.

**4.3 Contraindications**

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
* Severe hepatic insufficiency.

**4.4 Special warnings and precautions for use**

With reduced access to carbohydrate and high-quality protein, the safety margin for toxic liver reactions is smaller than with normal nutritional status. Continued use or maximum doses, especially in patients with poor nutritional status due to alcohol abuse, anorexia or malnutrition lead to an increased risk of liver damage. Treatment of febrile conditions in children should preferably be of short duration for the same reason.

A risk of renal injury in long-term use cannot be ruled out. Caution should be exercised if there is severe hepatic or renal injury.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Headache

During long-term use (> 3 months) of analgesics taken every other day or more often, headaches may develop or worsen. Headache induced by excessive consumption of analgesics should not be treated with an increased dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

**4.5 Interaction with other medicinal products and other forms of interaction**

The following medicinal products may require a dose adjustment in combination with Paracet (see below for more information):

* warfarin and other coumarin derivatives
* certain antiepileptic medicinal products (phenytoin, phenobarbital, carbamazepine)
* rifampicin
* St. John’s wort (*Hypericum perforatum*)
* probenecid
* lixisenatide (an anti-diabetic agent)

Pharmacodynamic interaction

Regular use and continuous dosage of over 1.5 – 2 g paracetamol daily can cause an increase in INR in patients using *warfarin and other coumarin derivatives.* A dose adjustment may be necessary during concomitant use of paracetamol and these anticoagulant agents.

Pharmacokinetic interactions

Enzyme-inducing medicinal products, such as *carbamazepine, phenytoin, phenobarbital* and *St. John’s wort (Hypericum perforatum)* can increase the hepatotoxicity of paracetamol. Hydantoin derivatives, barbiturates and their derivatives and carbamazepine can induce paracetamol metabolism. This leads to a reduced concentration of paracetamol (40%) and increased biotransformation to a hepatotoxic reactive metabolite. Adjustment of the paracetamol dose is not necessary as this can result in an increased risk of hepatotoxic effects.

*Isoniazid, rifampicin* and other anti-tubercular agents and combinations of these can affect the pharmacokinetics of paracetamol with possible potentiation of hepatotoxicity. The paracetamol dose should not exceed 3 grams per day.

*Probenecid* almost halves the clearance of paracetamol by inhibiting conjugation with glucuronic acid. This probably means that the dose of paracetamol can be halved when it is administered concomitantly with probenecid.

When paracetamol is taken 1-4 hours after administration of lixisenatide,this results in delayed absorption of paracetamol. Patients should therefore be made aware that it takes longer than usual (up to 2 hours) before onset of effect of paracetamol when it is taken in the first few hours after administration of lixisenatide.

*Resins such as colestyramine, colestipol and colesevelam* reduce the gastrointestinal absorption of paracetamol. Generally, paracetamol should be taken at least one hour before or at least four hours after taking the resin. If there is an acute need for paracetamol, the medicinal product can be taken even if the resin was taken less than four hours before, but in that case, it should be noted that the efficacy of paracetamol may be reduced.

*Ethanol* (long-term use) induces CYP1A2. This leads to increased production of the hepatotoxic paracetamol metabolite NAPQI. Therefore, it is an increased risk of hepatotoxicity with high ethanol consumption. Occasional consumption of small to moderate amounts of ethanol does not however increase the level of the hepatotoxic paracetamol metabolite NAPQI to a dangerous extent.

Caution should be taken when paracetamol is used concomitantly with *flucloxacillin*, as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

PregnancyA large amount of data on pregnant women indicate neither malformative, nor foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy, however it should be used at the lowest possible effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feedingParacetamol is excreted in breast milk, and the milk:plasma ratio is 1. It is estimated that a breast-fed infant receives <2% of the maternal dose. It is unlikely that breast-fed infants are affected.

**4.7 Effects on ability to drive and use machines**

No traffic warning.

Paracet has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**

The following frequency convention is used for the classification of undesirable effects:

Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100),

Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data)

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| --- |
| **Blood and lymphatic system disorders** |
| Rare: | Thrombocytopenia, leukopenia and haemolytic anaemia |
| **Immune system disorders** |
| Rare: | Hypersensitivity to the medicinal product |
| Very rare: | Anaphylaxis, hypersensitivity reactions of the skin such as pruritus, angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis |
| **Respiratory, thoracic and mediastinal disorders** |
| Very rare: | Bronchospasm in patients who are hypersensitive to acetylsalicylic acid or other NSAIDs |
| **Hepatobiliary disorders** |
| Rare: | Liver impairment |
| **Skin and subcutaneous tissue disorders** |
| Rare: | Allergic skin reactions, exanthema |

Very rare cases of serious skin reactions have been reported.

Liver impairment during use of paracetamol has occurred in alcohol abuse.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

Symptoms

Acute massive overdose of paracetamol can cause liver damage. There are few symptoms of overdose in the first 24 hours. Anorexia, nausea and vomiting may occur. Signs of liver damage usually begin within 36 hours in the form of pain in the upper abdominal region and increases in ALAT/ASAT, INR and bilirubin. Maximum liver toxicity develops within 3-4 days: hepatic encephalopathy, coagulation disturbances and hypoglycaemia. Acute renal failure may occur.

Toxicity

The most important risk factor is overdosing over time (for example, over several successive days). Repeated overdoses reduce resilience as the level of glutathione (in active, reduced form) can be lower than normal. Therefore, always determine first whether the overdose is due to a single intake or repeated intakes. Therapeutic use of paracetamol in the days before any overdose is also relevant and should normally be included when the toxic dose is calculated. All exposures above the toxic dose should be taken to hospital.

Toxic dose for adults and children > 3 months: 100 – 170 mg/kg per day, depending on age and the period over which the overdose was taken.

Children < 3 months: the national poison information centre should always be contacted if there is any suspicion of overdose. Premature infants and infants aged under 3 months are assumed to have an increased risk of toxicity.

Treatment

Consider gastric lavage and treatment with charcoal. Administer N-acetylcysteine as soon as possible after probable ingestion of a toxic dose, but the treatment can be started at any time during the course of intoxication, including after the patient has developed hepatic encephalopathy. Liver transplantation may be appropriate. Contact the national poison information centre if needed.

**4.10 Legal status**

HA18

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group:Analgesics, other analgesics and antipyretics, ATC code: N02BE01.

Pharmacodynamic effects

Paracetamol has a central and peripheral analgesic effect. Paracetamol has an antipyretic effect on the thermoregulatory centre in the hypothalamus. Paracetamol does not affect haemostasis and does not irritate the gastrointestinal mucosa.

Paracetamol depletes glutathione, which protects against the harmful effect of the reactive metabolite of paracetamol. A low glutathione level in exposed tissues predisposes to organ damage.

**5.2 Pharmacokinetic properties**

Absorption

Paracetamol is absorbed almost completely when administered rectally. The rate of absorption is somewhat slower than with oral administration. Therapeutic serum concentration is reached after approximately 1-1½ hours.

Distribution

Paracetamol is distributed rapidly and is distributed to most tissues. The volume of distribution is approx. 1 litre/kg. Protein binding is considered insignificant.

Biotransformation

Paracetamol is metabolised mainly to glucuronides and sulfate conjugates in the liver. A minor fraction is converted by a cytochrome P450-dependent oxidase to a highly reactive metabolite. This metabolite is rapidly inactivated on conjugation with reduced glutathione and is eliminated in the urine as acetylcysteine and mercapturic acid conjugates.

Elimination

The half-life of paracetamol is 2-3 hours. The half-life may be prolonged at toxic doses or in patients with liver damage.

Paracetamol is eliminated via the kidneys mainly as glucuronides with small quantities of sulfates and mercaptate and unchanged medicinal product. Approximately 85% of a paracetamol dose can be recovered in the urine as free and conjugated paracetamol within 24 hours after administration.

Patient factors

A serum concentration of 5-20 microg/ml paracetamol will produce an analgesic and antipyretic effect. A normal dose of paracetamol will be effective for 4-6 hours.

**5.3 Preclinical safety data**

Conventional studies conducted in accordance with currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Both unconverted paracetamol and active metabolites can bind to DNA and cause DNA damage. Studies from cell lines in culture, experimental animals and isolated human lymphocytes have shown that paracetamol can increase the incidence of chromosomal damage. Studies on lymphocytes from healthy volunteers following intake of therapeutic doses have produced contradictory results. Definitive conclusions cannot currently be drawn due to the design of the studies. Epidemiological studies have examined the correlation between use of paracetamol and development of cancer. There is no definitive evidence at present that paracetamol is carcinogenic to humans.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Hard fat

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

5 years.

**6.4 Special precautions for storage**

Do not store above 25 °C.

**6.5 Nature and contents of container**

Paracet suppositories are packed in torpedo-shaped plastic containers.

Pack sizes:

60 mg, 125 mg, 250 mg, 500 mg and 1 g: 10 suppositories

500 mg and 1 g: 50 suppositories

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Karo Pharma AS

Østensjøveien 27

Postboks 6733 Etterstad

0609 Oslo

Norge

**8. MARKETING AUTHORISATION NUMBER(S)**

60 mg: 71022

125 mg: 71023

250 mg: 71024

500 mg: 71025

1 g: 71026

**9. DATE OF FIRST AUTHORISATION**

15 January 2024

**10. DATE OF REVISION OF THE TEXT**

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